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Commentary

Sex differences in systemic lupus erythematosus: Epidemiology, clinical considerations, and disease pathogenesis

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic, multiorgan, systemic autoimmune disease that occurs more frequently in women than men and is typically diagnosed in women of reproductive age. Sex-based differences in the epidemiology, pathogenesis, and clinical presentation of SLE necessitate sex-specific considerations in clinical care. However, the biological mechanisms associated with these sex-specific differences are not fully understood. In this article, we describe recent findings related to sex-based differences in SLE pathogenesis and discuss relevant clinical considerations arising from these findings.

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multiorgan, systemic autoimmune disease with a prevalence of 20 to 150 cases per 100,000 in the United States [1]. SLE is one of the most sex-differentiated autoimmune diseases and is nearly 9 times more common in women than men [2]. Because SLE is most frequently diagnosed in women of reproductive age, the disease presents medical and psychosocial challenges that can result in significant complications in pregnancy and family planning [3,4].

Major differences exist in the clinical presentation of SLE in males and females. Male patients are more likely to be diagnosed at an older age, and more likely to have renal involvement, hematological manifestations, and greater disease severity overall [5]. Our understanding of the biological mechanisms that result in sex-dependent differences in the clinical presentation and course of SLE continues to expand; however, there is still much that is not fully understood. Toll-like receptor (TLR) expression, micro RNA (miRNA) expression, and gut microbiota composition differ between males and females and have emerged as areas of interest in the study of sex differences in SLE [6]. Recent studies have continued to expand upon these theories and provide further insight into the pathogenesis of SLE and its clinical manifestations.

Toll-Like Receptors

Sex-specific differences in TLR expression have been hypothesized to contribute to the higher prevalence of SLE in females. TLRs play an important role in innate immunity as pattern-recognition receptors. In SLE, TLRs recognize endogenous nucleic acids within antibody complexes to induce production of type I interferons [7]. Type I interferons have been identified as an important mediator in SLE pathogenesis, with increased expression of interferon inducible genes and high levels of IFN-α being found in subsets of SLE patients [8]. In females, TLR7 and TLR8 have been shown to evade X-chromosome inactivation (XCI), resulting in increased expression of gene products [9,10]. Recent studies have focused on identifying specific mutations that lead to upregulation of TLR7 and production of IFN-α.

One of the mechanisms driving upregulation of TLR7 is increased expression of the cathepsin S (CTSS) gene. CTSS normally plays an important role in selecting peptides for antigen presentation and loading peptides onto major histocompatibility complex (MHC) class II molecules [11,12]. Prior studies have demonstrated that increased CTSS expression in dendritic cells (DCs) leads to the destruction of known T cell epitopes, resulting in autoreactive T cells that are able to escape

negative selection [13]. Previous studies have also identified that CTSS expression is mediated by the transcription factor, Blimp-1. Knockout of the gene encoding Blimp-1 led to overexpression of CTSS and T cell autoreactivity in female mice, but not in male mice [14]. These findings suggest a sex-related component in the overexpression of CTSS in autoimmunity. A recent study further explored the role of CTSS overexpression in SLE pathogenesis through upregulation of TLR7. Investigators observed the spontaneous generation of SLE symptoms and increased IFN-α levels in CTSS-overexpressing transgenic (CTSS-TG) mice. Using pristane to induce SLE symptoms in both the CTSS-TG group and wild type (WT) group, investigators found that the CTSS-TG mice experienced more severe SLE symptoms and greater production of IFN-α and other cytokines compared to the WT mice. Western blot analysis of the sample's spleens demonstrated increased TLR7 expression in the CTSS-TG mice compared to the WT group [15]. These findings reveal that CTSS overexpression is in itself sufficient to induce SLE pathogenesis. Furthermore, CTSS overexpression was shown for the first time to be in involved in the upregulation of TLR7 and IFN-α.

Direct genetic mutation may also drive TLR upregulation. Until recently there has been limited evidence describing the role of specific TLR genetic variants in the pathogenesis of SLE, and no human SLE cases due to TLR7 variants had been previously reported. A recent study identified $TLR7^{Y264H}$ as a specific missense variant resulting in a gain of function mutation in TLR7 [16]. The variant was identified through whole-genome sequencing of a girl diagnosed with SLE at 7 years-old. The variant had an increased affinity for endogenous ligands and was shown to be sufficient to cause SLE when introduced into mice. These findings are the first to provide evidence directly linking genetic mutation in TLR7 to the pathogenesis of SLE.

Anifrolumab

Furthering our understanding of sex-based differences in TLR and IFN-α expression may lead to better treatments and clinical outcomes for both male and female patients. The first drugs targeting this pathway have already begun to reach the market. Anifrolumab is an anti-type I IFN-α receptor 1 monoclonal antibody recently approved for the treatment of SLE. In early studies, anifrolumab demonstrated a significant reduction (p=0.001) in moderate-to-severe baseline disease activity in 47.8% of patients based on the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA). By comparison only 31.5% of patients in the placebo group showed the same response [17]. When comparing treatment response in males and females, female patients treated with anifrolumab had a 17.7% greater BICLA response rate than females in the placebo group. By comparison, male patients treated with anifrolumab had a 5.0% greater BICLA response rate than males in the placebo group, though the number of male patients in the study was small (7% of the overall study population) [18]. Further studies are needed to determine if there are significant differences in anifrolumab response between males and females.

MicroRNAs

Sex-specific differences in miRNA expression may also contribute to the increased incidence of SLE in females. miRNAs are small-noncoding RNAs that play a vital role in gene regulation [19]. Several miRNAs have been shown to be differentially regulated by estrogen levels [20-23]. Recent studies have identified additional miRNAs that may play a role in SLE pathogenesis. Most recently, one study identified increased expression of miR-21, miR-25, and miR-186 in peripheral blood mononuclear cells of SLE patients. Increased expression of these miRNAs was positively correlated with SLE disease activity scores. Levels of miR-146a were also decreased in these same patients and were negatively correlated with estradiol levels and SLE disease activity scores [24]. These findings suggest that higher levels of estradiol may play a role in increased disease activity through modulation of certain miRNAs.

Other recent studies have found a positive correlation between expression of miR-181a and SLE disease activity and negative correlations between miR-223, miR-451a, and miR-125a and SLE disease activity [25-27]. These findings highlight the complex relationship between miRNA expression and SLE pathogenesis and may help identify future targets for therapeutic treatment. However, it still remains unclear whether sex-based differences in miRNA expression serve as a driving mechanism in SLE pathogenesis.

Understanding different miRNA expression patterns in male and female SLE patients may have a role in the diagnosis of preclinical SLE. Early diagnosis may enable clinicians to prevent disease progression and minimize certain organ manifestations. An analysis of 17 studies evaluated several miRNAs and found that miR-21 served as the best potential biomarker for diagnosis of SLE. miR-21 expression levels were 68% sensitive (95% CI, 62% to 74%) and 77% specific (95% CI, 69% to 84%) in diagnosing SLE [28]. However, miR-21 expression levels are known to be increased in several other autoimmune diseases; therefore, further studies are needed to determine if SLE patients have unique miRNA expression patterns that can be utilized for diagnosis [29].

Gut Microbiome

Sex-based differences in gut microbiota have recently emerged as another potential mechanism in SLE pathogenesis. The gut microbiome plays a key role in both the innate and adaptive immune systems, and gut microbiota dysbiosis may contribute to the pathogenesis of SLE and other autoimmune diseases [30-34]. It has also been hypothesized that the gut microbiota interacts with sex hormones to modulate autoimmune disease activity and progression [35-37]. Earlier studies have shown that early-life microbiome exposure plays a key role in determining sex hormone levels and modulating autoimmunity. One study utilized a nonobese diabetic (NOD) mouse model to transfer gut microbiota from NOD adult male mice to NOD immature female mice and found an elevation in testosterone levels [38]. The transfer of gut microbiota to NOD females prior to disease onset was also found to protect against pancreatic islet inflammation, autoantibody production, and the development of type 1 diabetes. Blocking androgen receptor activity was found to reverse this protection, thus suggesting that the microbiome is able to regulate sex hormone levels and provide protection to autoimmunity through androgen production.

Recent studies have investigated the role of sex-based differences in gut microbiota on SLE pathogenesis and disease activity. One study examined the effects of gut microbiota depletion in both male and female mice and observed a significant decrease in expression levels of pro-inflammatory cytokines in females that underwent gut microbiota depletion [39]. There were no significant differences in males that underwent depletion suggesting that the gut microbiota has a stronger influence on the immune phenotype in female mice.

Furthermore, microbiota transfer studies resulted in significantly slower SLE progression and reduced proteinuria when transferred from male to female mice. Mildly accelerated disease progression and increased proteinuria were noted after transfer from females to males. As a whole, these findings provide further evidence of the influence of the gut microbiota in SLE disease activity in male mice.

In addition to differences in gut microbiota composition, there may also be differences in immunoglobulin and antibody presence in the gut. Studies have shown higher levels of IgA in stool samples from SLE patients when compared to healthy controls [40]. IgA class anti-DNA antibodies have also been found in patients with SLE thus suggesting that these autoantibodies may originate from gut primed B cells [41-45]. Further analysis found that these IgA antibodies were higher in stool samples from lupus-prone mice. Moreover, IgA levels in female lupus-prone mice were particularly elevated and displayed significant reactivity towards nucleohistone and dsDNA nuclear antigens [44]. In the context of previous studies, these findings suggest that IgA production by the gut mucosa may contribute to the sex differences seen in SLE.

Treatment Considerations

Despite significant differences in the clinical presentation and disease course of SLE between females and males, there are generally few sex-specific differences in treatment of the disease. A recent longitudinal study tracked male and female patients with SLE for 20 years to determine whether there are differences in choice of treatment between males and females. Researchers found that mycophenolate mofetil was more frequently used in males than females (63% vs 36%, p=0.005) while antimalarials were less frequently prescribed to male patients (87% vs 97%, p=0.02) [46]. The authors suggested that mycophenolate mofetil may be more frequently prescribed to males because of increased rates of renal and neurological involvement in males. These differences in treatment, however, don't appear to relate to considerations of sex-specific differences in the biology of the disease.

In general, the most notable sex-specific treatment consideration is drug choice in female patients of childbearing age. Frequently used medications such as cyclophosphamide, methotrexate, and mycophenolate mofetil raise concerns for pregnancy complications, fetal abnormalities, and fetal loss. Optimal medical treatment of females of reproductive age requires early conversations about contraception, preconception planning, and pregnancy risk.

Conclusion

Our understanding of the biological mechanisms that underlie sex-related differences in SLE continues to expand with new insights into the expression of TLRs, regulation of miRNAs, and composition of the gut microbiota. Further study of these mechanisms and their interplay is essential to improving the lives of SLE patients.

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